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INVESTIGATIONS OF INTER- AND INTRA-INDIVIDUAL RELATIONSHIPS BETWEEN ABSORPTION OF ORAL SALMON CALCITONIN AND A SURROGATE MARKER OF PHARMACODYNAMIC EFFICACY

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Purpose: The aim of the study was to compare inter- and intra-individual bioavailability of 0.8 mg of oral salmon calcitonin (sCT) given once before or after food intake to assess the relationship between bioavailability and levels of the bone resorption biomarker, serum C-terminal telopeptide of collagen type I (CTX-I).
Methods: Participants were from two randomized, double-blind, placebo-controlled studies. Study I was a cross-over trial including healthy postmenopausal women receiving a single dose of 0.8 mg of oral sCT or placebo pre-breakfast at 08:00 (n=42), pre-dinner at 17:00 (n=20), or post-dinner at 22:00 (n=19). Blood samples were taken before drug intake, and at 5, 10, 15, 30, 45 minutes, 1, 1½, 2, 2½, 3 hours, and every subsequent hour until 24 hours after dosing. Study II investigated the pharmacokinetics and pharmacodynamics of oral sCT administered on days 1 and 14 to postmenopausal women and men (n=73) suffering from osteoarthritis (OA). In one treatment arm, 0.8 mg of oral sCT was given twice daily with one dose in the morning at 08:00 and one dose given pre-dinner at 17:00 (n=26). On treatment day 1 and day 14, blood samples were taken before drug intake, and at 10, 15, 30, 45 minutes, and 1, 2, and 4 hours post-dose. In both studies the absorption of calcitonin was assessed by plasma sCT concentrations, and bone resorption by the biochemical marker of serum CTX-I.
Results: Irrespective of dosing time, a single dose of 0.8 mg oral sCT was rapidly absorbed, reaching C_{max} between 15 to 30 minutes in both low and high absorbers. Following C_{max}, sCT was eliminated from plasma with a half-life between 9 and 15 minutes. Overall, a single dose of 0.8 mg oral sCT resulted in significant suppression of serum CTX-I compared with placebo irrespective of the level of absorption of sCT. At all three dosing times a significantly higher suppression of sCTX-I was observed in subjects with the highest intestinal absorption of sCT. The effect of increased absorption of sCT was a marked prolongation of serum CTX-1 suppression whereas acute suppression 1 to 2 hours after dosing was unaffected. A high degree of correlation between the level of absorption of sCT and the suppression of serum CTX-I was observed at all three dosing times, i.e. a Pearson correlation coefficient of r = -0.74, r = -0.94, and r = -0.78, was found at the dose times 08:00, 17:00, and 22:00. A weak association of borderline significance was found in the intra-individual absorption of sCT on dosing days 1 and 14 with r = 0.40 and r = 0.38 at the dose times 08:00 and 17:00. As expected, the intra-individual response in serum CTX-I levels was statistically non-significantly associated on dosing days 1 and 14 with r = 0.34 and r = 0.27 at the dose times 08:00 and 17:00.
Conclusions: Increased bioavailability of orally administered 0.8 mg sCT is highly correlated with suppression of the bone resorption marker, serum CTX-I. Moreover, the effect is highly controlled with a minimum of individual variability in serum CTX-I. The variable absorption of the drug demonstrates the importance of determining the optimal conditions for ensuring a most beneficial drug uptake.

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EXTRACORPOREAL SHOCKWAVE SHOWS REGENERATION IN HIP NECROSIS

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Purpose: The effect of shockwave in osteonecrosis of the femoral head (ONFH) is poorly understood. The purpose of this study was to investigate the regeneration effects of shockwave in ONFH.
Methods: This study consisted of 14 femoral heads from 14 patients undergoing total hip arthroplasty for ONFH. Seven patients with seven hips who received shockwave prior to surgery were designated as the study group, whereas, seven patients with seven hips who did not receive shockwave were assigned to the control group. Both groups showed similar demographic characteristics. The femoral heads were investigated with histopathological examination and immunohistochemical analysis with von Willebrand factor (vWF), VEGF, platelet endothelial cell adhesion molecule-1 (PECAM-1) also referred to as (CD 31) and vascular cell adhesion molecule (VCAM) for angiogenesis, and with proliferation cell nuclear antigen (PCNA), Dickkopf-1 (DKK1) and Winless 3a (Wnt 3) for bone remodelling and regeneration.
Results: In histopathological examination, the study group showed significantly more viable bone and less necrotic bone, higher cell concentration and more cell activities including phagocytosis than the control group. In immunohistochemical analysis, the study group showed significant increases in vWF ($P<0.01$), VEGF ($P<0.0012$) and CD 31 ($P<0.0023$), Wnt3 ($P<0.008$) and PCNA ($P<0.0011$), and decreases in VCAM ($P<0.0013$) and DKK1 ($P<0.0007$) than the control group.
Conclusions: Shockwave treatment significantly promotes angiogenesis and bone remodelling than the control. It appears that application of shockwave results in regeneration effects in hips with ONFH.

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CORE TEMPERATURE OF END-STAGE OSTEOARTHRITIC KNEE

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Purpose: Knee osteoarthritis (KOA) is one of the commonest joint diseases in an aged society. Among several complaints patients have, knee pain is most bothering to the patients. But the mechanisms concerning knee pain are poorly understood. Certain researchers refer to blood flow disturbance of the subchondral bone in KOA as possible cause of knee pain. Up until now, several studies have been performed about blood flow of bone marrow in femur and tibia, and controversial results have been reported. In the present study, we measured the core temperature of OA knees which is considered to reflect blood flow of deep structures.
Methods: End-stage KOA patients who were hospitalized and were waiting for total knee althroplasty (TKA) were involved in this study (n=16). As a control knees, healthy volunteers who had not had any knee symptoms were selected (n=10). Measurement of the core temperature of knee joint as well as sternum area was performed using Core-temp CM-210 (Terumo, Tokyo). With this apparatus core temperature was measured by simply attaching small metal probe to skin surface. (Zero-heat-flow method) Core temperatures of both groups of knees were monitored over night on ten-minute basis and compared. Moreover end-stage patients were divided into two groups: i.e.; those with night pain (N-group)

and those without night pain (WN-group) and core temperature of theirs was compared. Statistical analysis was performed using repeated measures ANOVA and p value less than 0.05 was considered as statistically significant.

Results: Core temperature of both the knee and the sternum decreased at around 5 am according to circadian rhythm.

Core temperature of the knee was significantly lower than that of the sternum in KOA. On the other hand, such difference was not seen in control knees.

Core temperature of the knee between N-group and WN-group was not different.

Conclusions: We revealed the lower core temperature of the knee in end-stage KOA. This indicated existence of blood flow disturbance in OA knees. Our data supports decreased bone perfusion in KOA exhibited with perfusion MRI. Elevated bone marrow pressure measured with invasive technique was also reported as one possible mechanisms of KOA pain and it might related to blood flow disturbance, though inconsistent results was reported about bone marrow pressure.

In the present study, we firstly reported blood flow disturbance in KOA by measuring core temperature. We only dealt end-stage OA patients in this study, but this non-invasive method might be useful in monitoring KOA status.

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DURATION OF A SINGLE INTRAARTICULAR INJECTION OF GEL-200 AND SAFETY OF RE-TREATMENT OF GEL-200, A NEW CROSS-LINKED FORMULATION OF HYALURONIC ACID [HA] IN THE TREATMENT OF SYMPTOMATIC OSTEOARTHRITIS [OA] OF THE KNEE

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Purpose: This was a randomized controlled trial (RCT) with extension and open-label re-treatment phases to determine if single or repeated intra-articular injections of Gel-200 are safe and effective in subjects with symptomatic knee osteoarthritis.

Methods: Subjects completing Week 13 in SI-6606/01 RCT were offered enrollment in extension phase, evaluating durability of responses relative to initial baseline for up to 13 weeks. If and when subjects qualified for re-treatment based on WOMAC pain subscore $\geq$40 mm in treated knee, they received a single injection of Gel-200 at Week R0 (open-label baseline). Survival analyses were conducted in Kaplan-Meier and Cox proportional hazard models to compare time to re-treatment eligibility using 2 different pre-specified endpoints: (A) WOMAC pain subscore $\geq$40 mm; and (B) WOMAC Pain $\geq$40 mm and improvement from baseline $<$20 mm.

Results: Of 350 completing SI-6606/01; 258 subjects entered extension: 199 subjects were re-treated with Gel-200; 74 analyzed for continued effectiveness. Kaplan-Meier estimates showed a statistically significant advantage for Gel-200 in both Endpoints A (p=0.049) and B (p=0.034). [Table] Median times to re-treatment eligibility were 6.3 weeks for subjects initially receiving Gel-200 compared with 3.7 weeks for PBS by (A), and 13.1 vs 6.0 weeks by Endpoint (B). In Cox proportional hazard models, Gel-200 showed statistically significant advantages in durability of response, using treatment, age, and baseline WOMAC pain subscore as covariates for Endpoints A (p=0.019) and B (p=0.027). All subjects receiving open label Gel-200 demonstrated improvement from Week R0 baseline in WOMAC scores (pain, stiffness, function, total), global assessments (subject, physician) ($P<0.0001$); incidence of adverse events [AEs] within 24 hours of injection were comparable to those observed in initial RCT. There were no allergic reactions or unanticipated device-related AE. Serious AE occurred in 6 subjects, none related to the study injection.

Survival Analysis - Kaplan-Meier Estimates

Weeks post injection in the SI-6606/01 study	Endpoint A (p=0.049)		Endpoint B (p=0.034)	
	Gel-200 (N=247)	PBS (N=128)	Gel-200 (N=247)	PBS (N=128)
Week 1	1.000	1.000	1.000	1.000
Week 3	0.952	0.941	0.961	0.942
Week 6	0.522	0.390	0.616	0.500
Week 9	0.473	0.355	0.560	0.441
Week 13	0.419	0.346	0.514	0.406
Week 16 (Week 3 in Extension phase)	0.292	0.264	0.387	0.342
Week 19 (Week 6 in Extension phase)	0.292	0.264	0.387	0.342
Week 22 (Week 9 in Extension phase)	0.280	0.264	0.375	0.342
Week 26 (Week 13 in Extension phase)	0.280	0.237	0.375	0.317

Conclusions: Together, these data support the efficacy and durability of response of a single intraarticular injection of Gel-200 over 13 weeks as treatment for knee osteoarthritis. This study also demonstrated that repeat treatment of Gel-200 was well tolerated.

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DOSE STABILITY OF TAPENTADOL EXTENDED RELEASE AND OXYCODONE CONTROLLED RELEASE IN A ONE-YEAR, RANDOMIZED, OPEN-LABEL, PHASE 3 SAFETY TRIAL IN PATIENTS WITH CHRONIC LOW BACK OR OSTEOARTHRITIS PAIN

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Purpose: To assess the long-term safety and effectiveness of tapentadol extended release (ER), a novel centrally acting analgesic in development for the management of moderate to severe chronic pain, over 1 year of treatment in patients with chronic low back or osteoarthritis pain.

Methods: Patients were randomized 4:1 to receive controlled, adjustable, oral bid doses of tapentadol ER 100-250 mg or oxycodone HCl controlled release (CR) 20-50 mg. In order to establish an optimal therapeutic dose, defined as a dose providing a balance of efficacy and tolerability, patients could titrate their doses in increments of 50-mg bid tapentadol ER or 10-mg bid oxycodone HCl CR during a 51-week maintenance period. Safety was assessed for all patients who received at least 1 dose of study medication.

Results: Patients received tapentadol ER (n = 894) or oxycodone CR (n = 224). The mean (standard deviation) and median most frequently used daily doses were 352.2 (132.43) mg and 400 mg with tapentadol ER and 56.8 (30.07) mg and 40 mg with oxycodone HCl CR. Patients who received tapentadol ER and oxycodone CR took the most frequently used dose for a median duration of 133.5 and 45.0 consecutive days, respectively. Patients in the oxycodone CR group discontinued treatment earlier than patients in the tapentadol ER group; in the first 4 weeks of the study, approximately 40% of patients in the oxycodone CR group discontinued treatment compared with approximately 20% of patients in the tapentadol ER group. The percentage of patients who discontinued because of adverse events (AEs) during the